

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Walhout et al.	Art Unit :	1636
Serial No. :	10/561,762	Examiner :	Michele K. Joike
Filed :	June 7, 2006	Conf. No. :	1626
Title :	HIGH THROUGHPUT ONE-HYBRID SYSTEM		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO ACTION OF JUNE 30, 2008

In reply to the Office Action of June 30, 2008, applicants submit the following remarks. Applicants are also submitting herewith a Petition for Extension of Time for two months, and an Information Disclosure Statement with the required fee.

Claim Rejections - 35 USC § 112

Claim 3 was rejected as allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Office action states that the yeast strain YM4271 does not appear to be publicly available. However, the specification states that strain YM4271 is available from BD Biosciences, Palo Alto, CA (see page 9, lines 12-13). Further, strain YM4271 is also available from the American Type Culture Collection (ATCC) as ATCC® Number 200808™ (deposit not made by applicants). Applicants submit that claim 3 complies with the enablement requirement and request withdrawal of the rejection.

Claim Rejections - 35 USC § 103

Claims 1-7 and 11-13 were rejected as being allegedly unpatentable over Walhout et al. (Methods Enzymol., 328:575-592, 2000) in view of Fields et al. (Nature, 340:245-246, 1989) and further in view of Sugawara et al. (Med. Sci. Monit., 8:BR431-438, 2002). Applicants respectfully traverse.

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The claimed methods include the use of two primary compositions. The first is a cell having integrated into its genome one or more bait-reporter constructs, wherein each construct includes a single copy of a bait element flanked by lambda recombination sites and a reporter gene. The second is an expression vector encoding a fusion protein having an activation domain, which is transformed into the cell having the bait-reporter constructs. This arrangement allows for detection of DNA-protein interactions by use of an improved one-hybrid type system. One-hybrid systems are based on the activation of reporter gene expression by a hybrid protein in which an open reading frame of interest is fused to the activation domain of a transcription factor. When the fusion protein binds to a promoter of interest through its cognate DNA binding domain, reporter gene expression is activated by the activation domain part of the fusion protein and can be efficiently selected for.

Walhout et al. generally discusses the cloning of *C. elegans* open reading frames (ORFs) and the determination of protein-protein interactions using a two-hybrid method. However, Walhout et al. does not teach or suggest the detection of DNA-protein interactions using a bait element of at least 250 base pairs flanked by lambda recombination sites. The present specification (at page 3, lines 12-14) defines a "bait element" as "a sequence of DNA that associates with, e.g., is bound by, a transcription factor," typically all or part of a promoter sequence. On the other hand, ORFs are nucleic acid sequences that encode proteins. Walhout et al. does use lambda recombination sites, but these sites are used for cloning ORFs, not for use with bait element sequences that associate with transcription factors. Further, Walhout et al. does not teach or suggest a cell with a bait element (or even an ORF) integrated into its genome. Although Walhout et al. uses lambda recombination sites for integration of ORFs (and not bait elements) into plasmids, these ORFs are never integrated into the genome of an organism. The cloning scheme is described at page 580 of Walhout et al.:

[A] PCR product containing the ORF of interest is recombined into a "Donor vector," using the BP reaction [recombination between attB and attP sites]. The resulting "Entry clone" is then used to recombine the ORF by the LR reaction [recombination between attL and attR sites] into one or more "Destination vectors," generating "Expression clones" (Fig. 2B; see color insert).

Walhout et al. further states that these recombination reactions take place *in vitro*, outside any cell or organism. Lastly, Walhout et al. neither teaches nor suggests determining whether an activator domain fusion protein has bound to a bait element.

Fields et al. does not remedy the deficiencies of Walhout et al. Fields et al. generally teaches a method of detecting protein-protein interactions using a two-hybrid system. Fields et al. does not teach or suggest the detection of DNA-protein interactions. Specifically, Fields et al. does not teach or suggest (i) a cell having integrated into its genome a bait-reporter construct with a single copy of a bait element flanked by lambda recombination sites or (ii) detecting the binding of an activator domain fusion protein to the bait element.

Sugawara et al. likewise does not remedy the deficiencies of Walhout et al. and Fields et al. for several reasons. Sugawara et al. generally discusses the use of a one-hybrid system to detect endocrine-disrupting compounds with the yeast strain YM4271. In this method, Sugawara et al. uses three tandem copies of an estrogen response element (ERE) reporter construct. Thus, even if the EREs were each considered a "bait element" as claimed, Sugawara's three EREs, do not teach or suggest use of a *single copy of a bait element* as claimed. In addition, each ERE is about 30 bp (see page BR432, second column, "Plasmid Constructs"). Altogether, the three tandem copies of the ERE would only come to about 90 bp, therefore Sugawara et al. does not teach or suggest a bait element having *at least 250 base pairs* as presently claimed. Further, Sugawara et al. fails to disclose or suggest the use of *lambda recombination sites*.

As discussed above, none of Walhout et al., Fields et al., or Sugawara et al. describes a cell whose genome includes one or more integrated bait-reporter constructs, wherein each of the one or more bait-reporter constructs includes (a) a single copy of a bait element having at least 250 base pairs flanked by lambda recombination sites, wherein the bait element comprises at least 250 base pairs, and (b) a reporter gene. Specifically, the ORFs discussed in Walhout et al. are not the equivalent of the bait element recited in the claims. Because the Office's alleged combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest every element of the claims, the Office has failed to establish a *prima facie* case of obviousness, and

the claims are patentable over the combination. Thus, applicants respectfully request reconsideration and withdrawal of the rejection for alleged obviousness.

Claim 8 was rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of Luo et al. As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. Luo et al. does not remedy the deficiencies of Walhout et al., Fields et al., and Sugawara et al. Luo et al. discloses a mammalian two hybrid system to detect protein-protein interactions. This system uses three plasmids, two of which express the interacting fusion proteins and the third containing a reporter construct. Luo et al. does not teach or suggest the detection of DNA-protein interactions, a cell with a bait-reporter construct integrated into its genome, or a bait element flanked by lambda recombination sites. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and Luo et al. fails to teach or suggest every element of the claims, and applicants request reconsideration and withdrawal of the rejection.

Claims 9 and 10 were rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of Chalfie et al. As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims, and Chalfie et al. does not remedy these deficiencies. Chalfie et al. describes the use of GFP as a transcriptional expression marker. However, Chalfie et al. does not teach or suggest the detection of DNA-protein interactions or a bait-reporter construct of any sort. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and Chalfie et al. fails to teach or suggest every element of the claims, and applicants request reconsideration and withdrawal of the rejection.

Claim 14 was rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of Cost et al. As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. Cost et al. does not remedy these deficiencies. While Cost et al. describes the use of MET15 as a reporter, it does not teach or suggest the

detection of DNA-protein interactions or a bait-reporter construct of any sort. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and Cost et al. fails to teach or suggest every element of the claims, and applicants request reconsideration and withdrawal of the rejection.

Claims 15 and 16 were rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of US 5,965,368 (the '368 patent). As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. The '368 patent does not remedy these deficiencies. The '368 patent generally discloses methods for identifying molecular interactions. According to the abstract of the '368 patent, "[a]ll of the methods within the invention employ counter-selection and at least two hybrid molecules." The '368 patent does not teach or suggest the claimed methods, which use only one hybrid molecule (a fusion protein comprising an activation domain, wherein binding of the fusion protein to the DNA bait element is detected). Further, the '368 patent does not teach or suggest a cell whose genome includes one or more integrated bait-reporter constructs, wherein each of the one or more bait-reporter constructs includes (a) a single copy of a bait element having at least 250 base pairs flanked by lambda recombination sites, wherein the bait element comprises at least 250 base pairs and (b) a reporter gene. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and the '368 patent fails to teach or suggest every element of the claims, and applicants request reconsideration and withdrawal of the rejection.

Claim 17 was rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of US 5,525,490 (the '490 patent). As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. The '490 patent does not remedy these deficiencies. The '490 patent generally teaches reverse two-hybrid systems to screen for molecules that can inhibit protein-protein interactions. The '490 patent does not teach or suggest the detection of DNA-protein interactions or a cell whose genome includes one or more integrated bait-reporter constructs, wherein each of the one or more bait-reporter constructs

includes (a) a single copy of a bait element having at least 250 base pairs flanked by lambda recombination sites, wherein the bait element comprises at least 250 base pairs and (b) a reporter gene. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and the '490 patent fails to teach or suggest every element of the claims, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

In light of the arguments made herein, applicants submit that the pending claims are patentable and request early and favorable action thereon. If the Examiner feels it would further prosecution of the present case, he is invited to telephone the undersigned at 617-521-7020.

Applicants do not concede any positions of the Office that are not expressly addressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This reply is being submitted along with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account 06-1050, referencing Attorney Docket No. 07917-0232US1.

Respectfully submitted,

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